IN THE UNITED STATES PATENT OFFICE

Application Serial No. 07/675,908

Filed: July 3, 1991

Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS DERIVATIVES TO ENHANCE DELIVERY OF ANTINEOPLASTIC AGENTS

Inventors: Dr. Rudolf Falk,
Dr. Samuel S. Asculai

Examiner: Dr. Jacqueline Krikorian Ph.D. (*formerly* Dr. Stephen Martin, Ph.D.)

Group Art Unit: 1806 Extended Due Date: September 5, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF STELLAN LIND
under § 1.132

I, STELLAN LIND, of Uppsala, Sweden hereby declare:

1. Marked as Exhibit 1 to this my Affidavit is a copy of my Curriculum Vitae. The reader will note that, while I have no scientific training with respect to hyaluronic acid, I have been employed by Pharmacia AB during the years 1980 to 1989. Pharmacia AB was the first and most successful in the development and marketing of hyaluronic acid (HA) based products. In this company, I was heavily involved in the area of dermatology as well as

other clinical applications. As a result, I acquired substantial knowledge and expertise in the state of knowledge of the industry of the uses of hyaluronic acid and effects of hyaluronic acid.

2. When I first became involved in this area during the period of 1980 to 1983, I learned from the best scientific expert at the time that HA was such a giant molecule that it could in no way penetrate the skin past the basal membrane but could serve as a water retention molecule in the very upper layer of stratum corneum.

3. As for use in the ophthalmics, Pharmacia developed Healon® which serves as a spacer and pusher of tissues and, at the time, was seen as a 100% inert material with no pharmacological effects whatsoever.

4. In 1987, Pharmacia established Pharmacia Biomaterials in order to commercialize HA outside ophthalmic use such as orthopedics by injection, middle ear surgery, and sperm preparation prior to in vitro fertilization. All work used the high molecular weight HA (>3 million daltons) that is a proprietary quality from Pharmacia.

5. In all three cases, orthopedics, middle ear surgery, and sperm preparation, the working principle was related to the physical/mechanical properties of HA.

6. In or about 1987, I also learned that HA, when applied topically for example, to the eye or skin, permitted a slow release of a substance carried by the HA for absorption by the eye or skin. In other words, if the substance in HA was applied topically, the HA would adhere to the eye or skin and permit the substance carried by the HA to leak therefrom and be absorbed by the local area to which it contacts. This type of approach is disclosed in U.S. Patent 4,736,024, a copy of which I was recently given for

consideration when preparing this my Declaration. Fidia SpA, the Patentee of U.S. Patent 4,736,024 may have been the source of the information learned in 1987. It has been some time now, however, I do recall such a formulation. We, at Pharmacia, looked at this technical area in general terms, however, no products were developed. To my knowledge, at the time no other participants in the industry developed any such products.

7. In or about 1985, one group in Pharmacia also investigated possible pharmaceutical effects of hyaluronic acid and gave injections of HA only to patients. Patients responded positively in the first clinical trial, however, the second trial gave the opposite result. We, at Pharmacia, thought that the benefits seen in the one study were not from HA but from some non-detectable residue of the HA left over from the manufacturing process that triggered the immune defence system. The project was closed. As a result, in about the years 1985 through 1987, we did not have any evidence of any pharmaceutical benefits whereby the HA could itself have a pharmacological effect. At all times, the HA, in our opinion, was passive and inert.

8. Studies were also undertaken for healing of the tympanic membrane using HA and adhesions in an animal model were treated with combinations of dextran and high molecular HA for which a patent was obtained. As for the positive healing results for the tympanic membrane, they were explained by the "scaffolding effect" of HA, i.e. a matrix on which new cells grow. In the prevention of adhesions, it was believed that the HA, and in the combination of dextran and HA, keep the tissues apart in the heart so that after the surgery performed around the heart no adhesions would occur. In addition, I was aware that another patent was obtained relating to a combination of fibrin glue and HA, which, once again, illustrated the physical/mechanical approach known in the '80's. In

my experience, with respect to the products offered for sale and being developed, it was never known or ever discussed that HA could be used as a drug delivery system other than topically and only to provide a depot. It was never known that HA could transport a drug to the site in need of treatment. Hyaluronic acid was always thought to provide mechanical/physical characteristics to any formulation and was essentially inert.

9. (a) When I first heard of Drs. Asculai and Falk's development and invention in or about 1990 to 1991 relating to the use of hyaluronic acid to deliver (transport) medicine and therapeutic agents to a site of disease or condition, in view of my past experience and knowledge in the industry, I thought that Drs. Asculai and Falk had got things absolutely wrong. I thought that this was not possible. To say I was very surprised is an understatement. Therefore, after hearing about this development in or about 1990/91, I went to Lennart Juhlin, Professor of Dermatology at Uppsala University to discuss. While I had always been told that big molecules such as hyaluronic acid could not possibly penetrate cell layers, and this was the position of the industry at that time, I was looking for an explanation. Professor Juhlin then explained what he called the "cement route", i.e. big molecules can penetrate between cells. Additionally, there are many big cells, I was advised, in the skin which do indeed penetrate. In any event, my view was now being changed.

(b) I have now been given a copy of International Publication No. WO 91/04058 and have been asked to review same. From my understanding of Drs. Asculai and Falk's development and invention, this application incorporates the invention of transporting (delivering) medicine and therapeutic agents to the site of a disease or condition.

10. Thus, whereas in the mid to late 80's when we, at Pharmacia, looked at hyaluronic acid, we thought that it went, if anything, into only the upper portion of the stratum corneum and remained on the surface, now things have changed. In fact, as I later learned, the hyaluronic acid targets the areas in the body deficient of hyaluronic acid because such areas have excess unfilled receptors for HA. Therefore, my present understanding with respect to intravenous injections is that the hyaluronic acid goes to the liver because the liver metabolizes HA. The liver on being "saturated", what is left over goes to the site of trauma or disease having excess hyaluronic acid receptors. The HA thus binds to the locations taking the medicine with it with some kind of binding. The ability to deliver medicines or therapeutic agents by this method was not known in 1989 and not expected in the industry. Thus, methods of treatment using the knowledge of the fact that HA could be used to treat diseases and conditions was, to my experience, not known. Thus, and as well, the dosages containing HA and a medicine or therapeutic agent to achieve these methods was not known. As taught by International Publication No. WO 91/04058, minimum amounts of HA are required with the medicines and therapeutic agents to delivery (transport) of the medicines and therapeutic agents. These minimum amounts of HA as described using smaller molecular weights (<750,000 daltons) of HA with medicines and therapeutic agents were not used, known, or taught, to my knowledge, in the industry. Because of my position in the industry, I would have expected to know if, in fact, they were used, known or taught.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the

knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 28th day of August, 1996.

STELLAN LIND

EXHIBIT 1

Curriculum Vitae

Name: Stellan Lind

Address: Artillerigatan 22
S-752 37 Uppsala
Sweden

Born: February 27, 1943

Education:

- 1968 Master of Business Administration, University of Uppsala.

Professional experience:

- 1968 Management Trainee, Unilever Group.
- 1970-72 Brands Analysis and Information Manager at Unilever Marketing Division, London.
- 1972-73 Product and Product Group Manager, Sunlight AB (Unilever detergents), Stockholm.
- 1976-79 President of IFH Research International AB, the Unilever Market Research company in Sweden.
- 1980-83 President of Pharmacia's Consumer Products Division, Uppsala, Sweden.
- 1984 President of Pharmacia's Dermatology and Tissue Repair Division.
- 1985-86 President of Pharmacia's Hospital Products Division.
- 1987-89 Head of Pharmacia Biomaterials, a research and business development unit for the commercialization of hyaluronic acid (HA) in other areas than ophthalmology. The unit focused on infertility treatment, orthopaedics and middle ear surgery.
- 1990-93 Following a buy-out of Pharmacia's patent for the use of HA in infertility treatment together with a Canadian colleague, establishing and running Select Medical Systems in the US and in Sweden.
- 1991 → Member of Hyal Pharmaceutical Corporation's International Advisory Panel.
- 1994 → Co-founder and President of Medisan Pharmaceuticals AB, a company based on the buy-out of Pharmacia's dextran based intravenous solutions business world wide, with sales of some 16 MUSD spending 2 MUSD on R&D.